At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of −70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. **1-3**. With reference to FIG. **1**, method of fill material **100** is shown. Step **102** comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step **104** comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **102** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step **106** comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **106** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2.

Step **108** comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step **110** comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **110** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Step **112** comprises degasing. The resulting mixture from step **112** may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. **2**, softgel capsule, i.e. gel mass, production **200** is shown. Step **202** comprises mixing glycercin with water. The water used in step **202** may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **202** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Heating may be performed until the temperature reaches 80° C.±5° C.

Step **204** comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **204** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. A vacuum may be drawn in step **204** to de-aerate.

Step **206** comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step **206** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Step **208** comprises degasing. The resulting mixture from step **208** may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. **3**, softgel capsule assembly process **300** is shown. Step **302** comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/−3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step **304** comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step **208** of FIG. **2**. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/−10° C. The wedge temperature may be 38° C.+/−3° C. The drum cooling temperature may be 4° C.+/−2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step **304** thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step **304** comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step **208** of FIG. **2**. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/−10° C. The wedge temperature may be 38° C.+/−3° C. The drum cooling temperature may be 4° C.+/−2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step **304** thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step **306** comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step **308** may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step **310** may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising:

a solubilizing agent comprising:

mono- and diglycerides of capric and caprylic acid; and

at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides;

progesterone; and

estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;

wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly dispersed.

2. The pharmaceutical composition of claim **1**, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.